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Title: ACOUSTO-MECHANICAL DETECTION SYSTEMS AND METHODS OF USE

1. ☒ Enclosed is the above-identified new provisional application for patent under 35 USC § 111(b)(1). It includes:
   - 26 Pages of Text
   - 4 Sheets of Informal Drawings
   - 62 Sheets of Appendix A (including cover sheet)
   - 6 Sheets of Appendix B (including cover sheet)
   - 11 Sheets of Appendix C (including cover sheet)
2. ☐ Enclosed is an executed Assignment to 3M Innovative Properties Company and a completed Assignment Recordation Cover Sheet.
3. ☒ This invention may have been made under a contract with an agency of the U.S. Government:
   Agency: Department of Defense
   Contract No. DAAD13-03-C-0047
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5. ☒ Please charge the $160.00 filing fee under 37 CFR § 1.16(k) to Deposit Account No. 13-3723. One copy of this sheet marked duplicate is also enclosed.
6. ☒ Please charge to Deposit Account No. 13-3723 any fees under 37 CFR §§ 1.16 and 1.17, which may be required to file and during the entire pendency of this application. This authorization includes the fee for any necessary extension of time under 37 CFR § 1.136(a). To the extent any such extension should become necessary, it is hereby requested.
7. ☒ Enclosed is a return receipt postcard.

Respectfully submitted,

December 30, 2003
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Filing of Papers and Fees by Express Mailing

Pursuant to 37 CFR § 1.10, this application and the documents and fees listed on this transmittal letter are being deposited on the date indicated below with the United States Postal Service "Express Mail Post Office to Addressee" service addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

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ACOUSTO-MECHANICAL DETECTION SYSTEMS AND METHODS OF USE

The present invention relates systems and methods for detecting one or more target biological analytes using acousto-mechanical energy.

Unlike classical clinical assays such as tube and slide coagulase tests, the present invention employs a biosensor. As used herein "biosensor" refers to a device that detects a change in at least one physical property and produces a signal in response to the detectable change. The manner in which the biosensor detects a change may include, e.g., electrochemical changes, optical changes, electro-optical changes, acousto-mechanical changes, etc. For example, electrochemical biosensors utilize potentiometric and amperometric measurements, whereas optical biosensors may utilize absorbance, fluorescence, luminescence and evanescent waves, and many of the systems suffer from a number of disadvantages when used to detect biological analytes.

In the case of acousto-mechanical biosensors, many biological analytes are introduced to the sensors in combination with a liquid carrier. The liquid carrier may undesirably reduce the sensitivity of the acousto-mechanical detection systems. Furthermore, the selectivity of such sensors may rely on properties that cannot be quickly detected, e.g., the test sample may need to be incubated or otherwise developed over time.

To address that problem, selectivity can be obtained by binding a target biological analyte to, e.g., a detector surface. Selective binding of known target biological analytes to detector surfaces can, however, raise issues when the biosensor used relies on acousto-mechanical energy to detect the target biological analyte.

One technical problem that is not addressed is the effect of the size and relative low level of mechanical rigidity of many or most biological analytes. This issue may be especially problematic in connection with shear-horizontal surface acoustic wave detection systems.

Shear horizontal surface acoustic wave sensors are designed to propagate a wave of acousto-mechanical energy along the plane of the biosensor detection surface. In some systems, a wave guide may be provided at the detection surface to localize the acousto-mechanical wave at the surface and increase the sensitivity of the sensor (as

compared to a non-wave-guided sensor). This modified shear horizontal surface acoustic wave is often referred to as a Love-wave shear horizontal surface acoustic wave biosensor ("LSH-SAW").

Such sensors have been used in connection with the detection of chemicals and other materials where the size of the target analytes is relatively small. As a result, the mass of the target analytes is largely located within the effective wave field of the sensors (e.g., about 60 nanometers (nm) for a sensor operating at a frequency of 103 Megahertz (MHZ)).

What has not heretofore been appreciated is that the effective wave field of the sensors is significantly limited relative to the size of biological analytes to be detected. For example, biological analytes that are found, e.g., in the form of single cell microorganisms, may have a typical diameter of, e.g., about 1 micrometer (1000 nm). As noted above, however, the effective wave field of the sensors is only about 60 nm. As a result, significant portions of the mass of the target analyte may be located outside of the effective wave field of the sensors.

In addition to the size differential, the target biological analytes are often membranes filled with various components including water. As a result, the effect of acousto-mechanical energy traveling within the effective wave field above a sensor on the total mass of the biological analytes can be significantly limited. In many instances, target biological analytes attached to the surfaces of such sensors cannot be accurately distinguished from the liquid medium used to deliver the agents to the detector.

Although not wishing to be bound by theory, it is theorized that the relative lack of mechanical rigidity in biological analytes attached to a detection surface, i.e., their fluid nature, may significantly limit the amount of mass of the biological analytes that is effectively coupled to the detection surface. In other words, although the biological analytes may be attached to the detection surface, a significant portion of the mass of the biological analyte is not acoustically or mechanically coupled to the acousto-mechanical wave produced by the sensor. As a result, the ability of an acousto-mechanical biosensor (e.g., a LSH-SAW biosensor) to effectively detect the presence or absence of target biological analytes can be severely limited.

SUMMARY OF THE INVENTION

The present invention provides detection systems and methods for detecting target biological analytes within a test sample using acousto-mechanical energy generated by a biosensor. The acousto-mechanical energy may preferably be provided using an acousto-mechanical sensor, e.g., a surface acoustic wave sensor such as, e.g., a shear horizontal surface acoustic wave sensor (e.g., a LSH-SAW biosensor), although other acousto-mechanical sensor technologies may be used in connection with the systems and methods of the present invention in some instances.

As discussed above, one issue that may be raised in the use of acousto-mechanical energy to detect the presence or absence of target biological analyte in a test sample is the ability to effectively couple the mass of the target biological analyte to the detection surface such that the acousto-mechanical energy from the sensor is affected in a detectable manner. The detection systems and methods of the present invention may, in some embodiments, provide a variety of techniques for modifying the effective mass of the target biological analytes in a test sample. The mass-modification techniques may include, e.g., fractionating or disassembling the target biological analytes in the test sample (e.g., lysing the target biological analyte), adding a detectable mass to the target biological analyte or enhancing coupling of the target biological analyte (e.g., through the use of magnetic particles), exposing the test sample to a reagent that causes a change in at least detectable physical property in the test sample if the target biological analyte is present (e.g., a viscosity change), etc.

Use of effective mass-modification techniques may, in some embodiments of the present invention, provide acousto-mechanical biosensors that may produce rapid, accurate results in the detection of various target biological analytes. As used herein, "target biological analyte" may include, e.g., microorganisms (e.g., bacteria, viruses, endospores, fungi, protozoans, etc.), proteins, peptides, amino acids, fatty acids, nucleic acids, carbohydrates, hormones, steroids, lipids, vitamins, etc.

The target biological analyte may be obtained from a test sample that is itself obtained by any suitable method and may largely be dependent on the type of target biological agent to be detected. For example, the test sample may be obtained from a subject (human, animal, etc.) or other source by, e.g., collecting a biological tissue and/or fluid sample (e.g., blood, urine, feces, saliva, semen, bile, ocular lens fluid, synovial fluid, cerebral spinal fluid, pus, sweat, exudate, mucous, lactation milk, skin,

hair, nails, etc.). In other instances, the test sample may be obtained as an environmental sample, product sample, food sample, etc. The test sample as obtained may be a liquid, gas, solid or combination thereof.

Before delivery to the systems and methods of the present invention, the test sample may be subjected to prior treatment, e.g., dilution of viscous fluids, concentration, filtration, distillation, dialysis, addition of reagents, chemical treatment, etc.

These and other features and advantages of the detection systems and methods of the present invention may be described in connection with various illustrative embodiments of the invention below.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a schematic diagram of one exemplary detection system according to the present invention.

FIG. 2 is a schematic diagram of another exemplary detection system according to the present invention.

FIG. 3 is a diagram of one flow cell that may be used in connection with the detection systems of the present invention.

FIG. 4 is a cross-sectional diagram of one fluid module that may be used in connection with the present invention.

FIG. 5 is a cross-sectional diagram of the fluid module of FIG. 4 during use.

FIG. 6A is a perspective view of a portion of one flow control surface that may be used in connection with the present invention.

FIG. 6B is a perspective view of a portion of another flow control surface that may be used in connection with the present invention.

FIG. 6C is a plan view of another flow control surface that may be used in connection with the present invention.

FIG. 6D is a plan view of another flow control surface that may be used in connection with the present invention.

FIG. 7 is a schematic diagram of one system that may be used in connection with the present invention.

FIG. 8 is a schematic diagram of the construction of one exemplary acousto-mechanical sensor that may be used in connection with the present invention.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS OF THE INVENTION

In the following detailed description of exemplary embodiments of the invention, reference is made to the accompanying figures of the drawing which form a part hereof, and in which are shown, by way of illustration, specific embodiments in which the invention may be practiced. It is to be understood that other embodiments may be utilized and structural changes may be made without departing from the scope of the present invention.

Some potentially suitable examples of the systems and/or methods of the invention may be described in various aspects in the attached appendices. For example, some systems and methods that may be within the scope of the present invention may be described in attached Appendix A entitled "Integrated Biosensor." Although in some instances, the exemplary systems and/or methods may be described in absolute or preferred terms, it should be understood that these absolute or preferred terms should not be construed to limit the present invention unless otherwise indicated herein.

The systems and methods of the present invention detect the presence of target biological analyte in a test sample through the use of acousto-mechanical energy. The acousto-mechanical energy may be generated using, e.g., piezoelectric-based surface acoustic wave (SAW) devices. As described in, e.g., U.S. Patent No. 5,814,525 (Renschler et al.), the class of piezoelectric-based acoustic mechanical devices can be further subdivided into surface acoustic wave (SAW), acoustic plate mode (APM), or quartz crystal microbalance (QCM) devices depending on their mode of detection.

In some embodiments, the systems and methods of the present invention may be used to detect a target biological analyte attached to a detection surface. In other embodiments, the devices may be used to detect a physical change in a liquid (e.g., an aqueous solution), such as, e.g., a change in viscosity, that is indicative of the presence of the target biological analyte. The propagation velocity of the surface wave is a sensitive probe that may be capable of detecting changes such as mass, elasticity, viscoelasticity, conductivity and dielectric constant in a medium in contact with the detection surface of an acousto-mechanical sensor. Thus, changes in one or more of these (or potentially other) physical properties may result in changes in the attenuation of the surface acoustic wave.

APM devices operate on a similar principle to SAW devices, except that the acoustic wave used can be operated with the device in contact with a liquid. Similarly, an alternating voltage applied to the two opposite electrodes on a QCM (typically AT-cut quartz) device induces a thickness shear wave mode whose resonance frequency changes in proportion to mass changes in a coating material.

The direction of the acoustic wave propagation (e.g., in a plane parallel to the waveguide or perpendicular to the plane of the waveguide) may be determined by the crystal-cut of the piezoelectric material from which the biosensor is constructed. SAW biosensors in which the majority of the acoustic wave propagates in and out of the plane (e.g., Rayleigh wave, most Lamb-waves) are typically not employed in liquid sensing applications because of acoustic damping from the liquid in contact with the surface.

For liquid sample mediums, a shear horizontal surface acoustic wave biosensor (SH-SAW) may preferably be used. SH-SAW sensors are typically constructed from a piezoelectric material with a crystal-cut and orientation that allows the wave propagation to be rotated to a shear horizontal mode, i.e., parallel to the plane defined by the waveguide, resulting in reduced acoustic damping loss to a liquid in contact with the detection surface. Shear horizontal acoustic waves may include, e.g., thickness shear modes (TSM), acoustic plate modes (APM), surface skimming bulk waves (SSBW), Love-waves, leaky acoustic waves (LSAW), and Bleustein-Gulyaev (BG) waves.

In particular, Love wave sensors may include a substrate supporting a SH wave mode such as SSBW of ST quartz or the leaky wave of 36°YXLiTaO$_3$. These modes may preferably be converted into a Love-wave mode by application of thin acoustic guiding layer or waveguide. These waves are frequency dependent and can be generated if the shear wave velocity of the waveguide layer is lower than that of the piezoelectric substrate.

Waveguide materials may preferably be materials that exhibit one or more of the following properties: low acoustic losses, low electrical conductivity, robustness and stability in water and aqueous solutions, relatively low acoustic velocities, hydrophobicity, higher molecular weights, highly cross-linked, etc. In one example, SiO_2 has been used as an acoustic waveguide layer on a quartz substrate. Examples of other thermoplastic and crosslinked polymeric waveguide materials include, e.g.,

epoxy, polymethylmethacrylate, phenolic resin (e.g., NOVALAC), polyimide, polystyrene, etc.

Alternatively, QCM devices can also be used with liquid sample mediums. Biosensors employing acousto-mechanical devices and components may be described in, e.g., U.S. Patent Nos. 5,076,094 (Frye et al.); 5,117,146 (Martin et al.); 5,235,235 (Martin et al.); 5,151,110 (Bein et al.); 5,763,283 (Cernosek et al.); 5,814,525 (Renschler et al.); 5,836,203 (Martin et al.); and 6,232,139 (Casalnuovo et al.). Shear horizontal SAW devices can be obtained from various manufacturers such as Sandia Corporation, Albuquerque, New Mexico. Some SH-SAW biosensors that may be used in connection with the present invention may also described in Branch et al., "Low-level detection of a *Bacillus anthracis* simulant using Love-wave biosensors on 36°YX $LiTaO_3$," Biosensors and Bioelectronics (accepted 22 August 2003).

EFFECTIVE MASS-MODIFICATION

As discussed herein, effective detection of target biological analyte in a test sample using acousto-mechanical biosensors may rely on modification of the effective detectable mass of the target biological analyte within a test sample. Some mass-modification techniques used in connection with the present invention may include, but are not limited to, e.g., fractionating or disassembling the target biological analyte in the test sample, adding a detectable mass to the target biological analyte, exposing the test sample to a reagent that causes a change in at least detectable physical property in the test sample if the target biological analyte is present. Examples of these approaches may be discussed in more detail below and/or in the attached appendices.

Fractionating/Disassembling:

The mass modification of the target biological analyte in connection with the systems and methods of the present invention may preferably take the form of, e.g., fractionating or otherwise disassembling the target biological analyte such that an increased percentage of the mass of the target biological analyte can be retained within the effective wave field of the acousto-mechanical sensor and/or effectively coupled with the detection surface of the acousto-mechanical sensor.

The fractionating or disassembly may be accomplished chemically, mechanically, thermally, or through combinations of two or more such techniques.

Examples of some potentially suitable chemical fractionating techniques may involve, e.g., the use of one or more enzymes, hypertonic solutions, hypotonic solutions, detergents, etc. Examples of some potentially suitable mechanical fractionating techniques may include, e.g., exposure to sonic energy, mechanical agitation (e.g., in the presence of beads or other particles to enhance breakdown), etc. Thermal fractionating may be performed by, e.g., heating the target biological agent. Other fractionating/disassembly techniques may also be used in connection with the present invention.

Magnetic Particle Attachment:

In another approach, mass-modification of the target biological analyte in connection with the systems and methods of the present invention may take the form of adding detectable mass to a target biological analyte using, e.g., magnetic particles, etc. with selective affinity to the target biological analyte. In such a system, a magnetic field may be established proximate the detection surface such that the mass-modified target biological analytes are attracted and attached to the detection surface where they can be detected by the acousto-mechanical sensor.

The magnetic particles can increase the effective mass of the target biological analyte by, e.g., drawing more of the target biological analyte into the effective acoustic wave field of the acousto-mechanical sensor. In other instances, the magnetic particles may modify the mechanical rigidity of the target biological analyte, thereby rendering it more easily detectable by the acousto-mechanical sensor. Selectively attached magnetic particles themselves may also provide additional mass to the target biological analyte to enhance detection. Still another potential effect of using magnetic particles in connection with the present invention is that the magnetic particles may, in some instances, provide a faster test by driving the target biological analyte to the detection surface under the influence of a magnetic field.

General methods of using magnetic particles and methods of making magnetic particles may be described in, e.g., U.S. Patent No. 3,970,518 (Giaever); U.S. Patent No. 4,001,197 (Mitchell et al.); and EP Publication No. 0016552 (Widder et al.). These methods may be adapted for use in connection with the present invention.

Test Sample Property Change:

In yet another approach, the mass-modification may involve exposing the test sample to a reagent that causes a change in at least detectable physical property in the test sample if the target biological analyte is present. The detectable physical change is essentially a mass-modification in that it may preferably increase the effective detectable mass of the target biological analyte. Such a change may be, e.g., a change in viscosity of the test sample. Although a change in viscosity is not technically considered a change in mass, it can change the effective detectable mass of the test sample because the mass located within the effective wave field can be more easily detected if its viscosity is decreased.

Examples of some suitable mass-modification techniques may be, e.g., the use of fibrinogen in combination with staphylococcus as described in, e.g., U.S. Patent Application No. _____, titled STAPHYLOCOCCUS DETECTION, filed on even date herewith (Attorney Docket No. 58930US002).

SELECTIVE ATTACHMENT

The detection systems and methods of the present invention may preferably provide for the selective attachment of target biological analyte to the detection surface or to another component that can be coupled to the detection surface. Regardless of whether the selective attachment of the target biological analyte is to the detection surface itself or to another component, it may be preferred that the mass coupled to the detection surface be capable of detection using acousto-mechanical energy.

Selective attachment may be achieved by a variety of techniques. Some examples may include, e.g., antigen-antibody binding; affinity binding (e.g., avidin-biotin, nickel chelates, glutathione-GST); covalent attachment (e.g., azlactone, trichlorotriazine, phosphonitrilic chloride trimer or N-sulfonylaminocarbonyl-amide chemistries); etc.

The selective attachment of a target biological analyte may be achieved directly, i.e., the target biological analyte may itself be selectively attached to the detection surface. Examples of some such direct selective attachment techniques may include the use of capture agents, e.g., antigen-antibody binding (where the target biological analyte itself includes the antigen bound to an antibody immobilized on the detection surface), etc.

Alternatively, the selective attachment may alternatively be indirect, i.e., where the target biological analyte is selectively attached to a carrier that is selectively attached or attracted to the detection surface. One example of an indirect selective attachment technique may include, e.g., selectively binding magnetic particles to the target biological analyte such that the target biological analyte can be magnetically attracted to and retained on the detection surface.

In connection with selective attachment, it may be preferred that systems and methods of the present invention provide for low non-specific binding of other biological analytes or materials to, e.g., the detection surface. Non-specific binding can adversely affect the accuracy of results obtained using the detection systems and methods of the present invention. Non-specific binding can be addressed in many different manners. For example, biological analytes and materials that are known to potentially raise non-specific binding issues may be removed from the test sample before it is introduced to the detection surface. In another approach, blocking techniques may be used to reduce non-specific binding on the detection surface. Examples of some blocking techniques may be described in Appendix B attached hereto (titled "Exemplary Immobilization Technologies").

Because selective attachment may often rely on coatings, layers, etc. located on the acousto-mechanical detection surface, care must be taken that these materials are relatively thin and do not dampen the acousto-mechanical energy to such a degree that effective detection is prevented.

Another issue associated with selective attachment is the use of what are commonly referred to as "immobilization" technologies that may be used to hold or immobilize a capture agent on the surface of, e.g., the acousto-mechanical sensor itself. The detection systems and methods of the present invention may involve the use of a variety of immobilization technologies.

As discussed herein, the general approach is to coat or otherwise provide the detection surface of an acousto-mechanical sensor device with capture agents such as, e.g., antibodies, peptides, aptamers, or any other capture agent that has high affinity for the target biological analyte. The surface coverage and packing of the capture agent on the surface may determine the sensitivity of the sensor. The immobilization chemistry that links the capture agent to the detection surface of the sensor may play a role in the

packing of the capture agents, preserving the activity of the capture agent (if it is a biomolecule), and may also contribute to the reproducibility and shelf-life of the sensor.

If the capture agents are proteins or antibodies, they can nonspecifically adsorb to a surface and lose their ability (activity) to capture the target biological analyte. A variety of immobilization methods may be used in connection with acousto-mechanical sensors to achieve the goals of high yield, activity, shelf-life and stability. These capture agents may preferably be coated using glutaraldehyde cross-linking chemistries, entrapment in acrylamide, or general coupling chemistries like carbodiimide, epoxides, cyano bromides etc.

Apart from the chemistry that binds to the capture agent and still keeps it active, there are other surface characteristics of any immobilization chemistries used in connection with the present invention that may need to be considered and that may become relevant in an acousto-mechanical sensor application. For example, the immobilization chemistries may preferably cause limited damping of the acousto-mechanical energy such that the immobilization chemistry does not prevent the sensor from yielding usable data. The immobilization chemistry may also determine how the antibody or protein is bound to the surface and, hence, the orientation of the active site of capture. The immobilization chemistry may preferably provide reproducible characteristics to obtain reproducible data and sensitivity from the acousto-mechanical sensors of the present invention.

Some immobilization technologies that may be used in connection with the systems and methods of the present invention may be described in, e.g., U.S. Patent Application No. 10/713,174, filed November 14, 2003, entitled N-SULFONYLAMINOCARBONYL CONTAINING COMPOUNDS (Attorney Docket No. 58627US002); U.S. Patent Application No. _____, filed on even date herewith, entitled SUBSTRATES AND COMPOUNDS BONDED THERETO (Attorney Docket No. 59355US002); and U.S. Patent Application No. _____, filed on even date herewith, entitled SUBSTRATES AND COMPOUNDS BONDED THERETO (Attorney Docket No. 59356US002).

Potential immobilization technologies that may be used in connection with the systems and methods of the present invention may include, e.g., those described in attached Appendix A, entitled "Integrated Biosensor" and attached Appendix B, entitled "Exemplary Immobilization Chemistries."

Many of the immobilization approaches may preferably include a tie layer between the waveguide on an acousto-mechanical substrate and the immobilization layer. One exemplary tie layer may be, e.g., a layer of diamond-like glass, such as described in International Publication No. WO 01/66820 A1 (David et al.). Diamond-like glass is typically considered an amorphous material that includes carbon, silicon, and one or more elements selected from hydrogen, oxygen, fluorine, sulfur, titanium, or copper. Some diamond-like glass materials are formed from a tetramethylene silane precursor using a plasma process. A hydrophobic material can be produced that is further treated in an oxygen plasma to control the silanol concentration on the surface.

Diamond-like glass can be in the form of a thin film or in the form of a coating on another layer or material in the substrate. In some applications, the diamond-like glass can be in the form of a thin film having at least 30 weight percent carbon, at least 25 weight percent silicon, and up to 45 weight percent oxygen. Such films can be flexible and transparent. In some multilayer substrates, the diamond-like glass is deposited on a layer of diamond-like carbon. The diamond-like carbon can, in some embodiments, function as a second tie layer or primer layer between a polymeric layer and a layer of diamond-like glass in a multilayer substrate. Diamond-like carbon films can be prepared, for example, from acetylene in a plasma reactor. Other methods of preparing such films are described U.S. Patent Nos. 5,888,594 and 5,948,166 (both to David et al.), as well as in the article by M. David et al., AlChE Journal, 37 (3), 367-376 (March 1991).

EXEMPLARY DETECTION SYSTEMS/METHODS

Some illustrative exemplary embodiments of systems and methods according to the principles of the present invention are described below in connection with various figures.

FIG. 1 a block diagram of one detection system according to the present invention. The system 10 includes inputs 22, 24, and 26. In the depicted system, the inputs may include a lysing agent 22, test sample 24, and wash buffer 26. These various components may be introduced into, e.g., a preparation chamber 28 where the various components may intermix and/or react with each other. For example, it may be desirable that the lysing agent 22 and test sample 24 be introduced into the preparation chamber 28 to allow the lysing agent 22 to act on the test sample 24 such that any target

biological analyte within the test sample 24 can be effectively lysed. Alternatively, one or more these components may be present in the preparation chamber 28 before one or more of the other components are introduced therein.

It may be preferred that the lysing agent 22 be selective to the target biological analyte, i.e., that other biological analytes in the test sample 24 are not lysed by the lysing agent. Alternatively, the lysing agent 22 may be non-selective, i.e., it may act on a number of biological analytes in the test sample 24, regardless of whether the biological analytes are the target biological analyte or not.

After lysing of the target biological analyte in the test sample 24, the lysing agent 22 and test sample 24 may be moved from the preparation chamber 28 to the detection chamber 30 where the target biological analyte in the test sample 24 can contact the detection surface 32. In the depicted system, the detection surface 32 may preferably be of the type that includes capture agents located thereon such that the target biological analyte in the test sample 24 is selectively attached to the detection surface 32.

In various systems and methods of the present invention, e.g., that depicted in FIG. 1, it may be beneficial to provide some control over test sample introduction to, flow rate over, and dwell time on the detection surface 32. In some instances, for example, it may be desirable to prevent the introduction of gas bubbles to the detection surface 32 if the test sample 24 is in liquid form. Another test sample control issue may be, e.g., controlling the flow rate of the test sample 24 over the detection surface 32. If the flow rate is too fast, the target biological analyte in the test sample 24 may not be accurately detected because selective attachment may be reduced or prevented. Conversely, if the flow rate is too slow, excessive non-specific binding of non-targeted biological analytes or other materials to the detection surface 32 may occur.

Fluid control on the detection surface may be addressed by a variety of techniques (either alone or in combination). Potential approaches include, e.g., surface flow control (using channels or other features), material properties (e.g., using hydrophilic or hydrophobic materials, coatings, etc.), using permeable membranes to control flow towards or away from the detection surface, etc.

After the target biological analytes in the test sample 24 have been resident in the detection chamber 30 for a sufficient period of time or have moved therethrough, a wash buffer 26 may be introduced into the detection chamber 30 to remove unattached

biological analytes and other materials from the detection chamber 30. These materials may preferably move into a waste chamber 36 connected to the detection chamber 30.

Detection of any target biological analytes selectively attached to the detection surface preferably occurs using the sensor 34 as operated by a control module 35. The control module 35 both operates the sensor 34 such that the appropriate acousto-mechanical energy is generated and monitors the sensor 34 such that an accurate determination of the presence or absence of the target biological analyte on the detection surface 32 can be made.

Examples of techniques for driving and monitoring acousto-mechanical sensors such as those that may be used in connection with the present invention may be found in, e.g., U.S. Patent Nos. 5,076,094 (Frye et al.); 5,117,146 (Martin et al.); 5,235,235 (Martin et al.); 5,151,110 (Bein et al.); 5,763,283 (Cernosek et al.); 5,814,525 (Renschler et al.); 5,836,203 (Martin et al.); and 6,232,139 (Casalnuovo et al.), etc. Further examples may be described in, e.g., Branch et al., "Low-level detection of a *Bacillus anthracis* simulant using Love-wave biosensors on 36°YX $LiTaO_3$," Biosensors and Bioelectronics (accepted 22 August 2003); as well as in U.S. Patent Application No. _____, filed on even date herewith, titled ESTIMATING PROPAGATION VELOCITY THROUGH A SURFACE ACOUSTIC WAVE SENSOR (Attorney Docket No. 58927US002) and in the attached Appendix A entitled "Integrated Biosensor."

Although the system 10 depicted in FIG. 1 uses a lysing agent 22 to fractionate or disassemble the target biological analyte, it should be understood that a similar system may be used if, e.g., the detection process relies on detectable change in a physical property of the test sample. For example, the lysing agent 22 may be replaced by, e.g., fibrinogen in a system/method such as that discussed in, e.g., U.S. Patent Application No. _____, titled STAPHYLOCOCCUS DETECTION, filed on even date herewith (Attorney Docket No. 58930US002). Also, although the depicted system uses a lysing agent, it will be understood that any suitable fractionating/disassembly agent and/or process (e.g., chemical, mechanical, thermal, etc.) may be used in place of a lysing agent.

Also, although the systems and methods of the present invention may be described herein in terms of a "detection surface," acousto-mechanical sensors used in connection with the present invention may preferably include one or more detection

surfaces, one of which may serve as a reference if desired. Within a single detection surface, two or more channels may be provided, one or more of which may be active, i.e., may be used to detect a target biological analyte. Optionally, one or more of the channels on a single detection surface may serve as a reference channel to provide a baseline or control against which the active channel or channels can be compared.

An alternative exemplary detection system is depicted in FIG. 2. The system 110 of FIG. 2 includes inputs 122, 124, 126, and 127. In the depicted system, the inputs include an optional lysing agent 122, test sample 124, optional wash buffer 126, and magnetic particles 127. These various components may be introduced into, e.g., a preparation chamber 128 where the various components may intermix and/or react with each other. Alternatively, one or more these components may be present in the preparation chamber 128 before one or more of the other components are introduced therein.

For example, it may be desirable that a lysing agent 122 and the test sample 124 be introduced into the preparation chamber 128 to allow the lysing agent 122 to act on the test sample 124 such that the target biological analyte within the test sample 124 can be effectively lysed. Following that, the magnetic particles 127 may be introduced into the preparation chamber 128. The magnetic particles 127 may preferably selectively attach to the target biological analytes (or their lysed fractions if so provided) within the preparation chamber 128.

The attachment of biological analytes to, e.g., magnetic particles, may be described generally in, e.g., International Publication Nos. WO 02/090565 (Ritterband) and WO 00/70040 (Bitner et al.) which describe the use of magnetic beads in kits to concentrate cells, as well as magnetically responsive particles. Selective attachment of a biological agent to magnetic particles (e.g., paramagnetic microspheres) is also described in, e.g., Kim et al., "Impedance characterization of a piezoelectric immunosensor part II: *Salmonella typhimurium* detection using magnetic enhancement," Biosensors and Bioelectronics 18 (2003) 91-99.

After selective attachment of the target biological analyte in the test sample 124 to the magnetic particles 127, the test sample 124 (and associated magnetic particles) may be moved from the preparation chamber 128 to the detection chamber 130 where the target biological analyte in the test sample 124 can contact the detection surface 132. Because the target biological analyte is associated with magnetic particles, it may

be desirable to include a magnetic device 133 capable of generating a magnetic field at the detection surface 132 such that the target biological analyte associated with magnetic particles can be retained on the detection surface for detection using sensor 134 operated by controller 135.

The use of magnetic particles in connection with the target biological analyte may enhance detection by, e.g., moving the target biological analyte to the detection surface 132 more rapidly than might be expected in the absence of, e.g., magnetic attractive forces.

If the detection surface 132 includes selective capture agents located thereon such that the target biological analyte is selectively attached to the detection surface 132 in the absence of magnetic fields, then the magnetic particles that are not carrying (or being carried by) any target biological analyte can be removed from the detection surface 132 by, e.g., removing the magnetic field and washing the detection surface 132. Washing the detection surface 132 in the absence of a magnetic field may preferably remove any magnetic particles that are not carrying (or being carried by) target biological analytes. Further, the target biological analyte (and the magnetic particles that are associated therewith) may preferably be retained on the detection surface 132 after washing in the absence of a magnetic field by the selective capture agent or agents on the detection surface 132.

Other methods of removing non-associated magnetic particles, i.e., magnetic particles that are not associated with any target biological analyte, may be performed before introducing the associated magnetic particles (i.e., magnetic particles carrying or being carried by target biological analyte).

Although two exemplary systems that may be used in connection with the present invention are discussed above, various components that may be well-suited to use in such systems will now be described in more detail. Those components include, e.g., an exemplary flow cell depicted schematically in FIG. 3. One example of a fluid module that may be used in connection with, e.g., the flow cell of FIG. 3 is depicted in connection with FIGS. 4 & 5. The fluid module may be used to store and/or introduce various components such as fractionating/disassembly agents, magnetic particles, reagents, wash buffers, etc. into systems of the present invention.

Turning first to the exemplary flow cell depicted in FIG. 3, the flow cell 40 may include a detection chamber 30 located therein, with a detection surface 32 facing the

volume of the detection chamber 30. The detection surface 32 is preferably formed on an acousto-mechanical sensor 34 that may preferably be, e.g., a Love wave shear horizontal surface acoustic wave sensor as described herein. As depicted, the sensor 34 may preferably be attached such that its backside, i.e., the surface facing away from the detection chamber 30, does not contact any other structures within the flow cell 40. Examples of some exemplary methods of attaching acousto-mechanical sensors within a system that may be used in connection with the present invention may be found in, e.g., U.S. Patent Application No. _____, filed on even date herewith and titled SURFACE ACOUSTIC WAVE SENSOR ASSEMBLIES (Attorney Docket No. 58928US002).

The flow cell 40 as depicted also includes an optional preparation chamber 28 into which various components may be introduced before entering the detection chamber 30. Although not depicted, it should be understood that the preparation chamber 28 could include a variety of features such as, e.g., one or more reagents located therein (e.g., dried down or otherwise contained for selective release at an appropriate time); coatings (e.g., hydrophilic, hydrophobic, etc.); structures/shapes (that may, e.g., reduce/prevent bubble formation, improve mixing, etc.).

Also, the fluid path between the preparation chamber 28 and the detection chamber 30 may be open as depicted in FIG. 3. Alternatively, the fluid path between the preparation chamber 28 and the detection chamber 30 may include a variety features that may perform one or more functions such as, e.g., filtration (using, e.g., porous membranes, size exclusion structures, beads, etc.), flow control (using, e.g., one or more valves, porous membranes, capillary tubes or channels, flow restrictors, etc.), coatings (e.g., hydrophilic, hydrophobic, etc.), structures/shapes (that may, e.g., reduce/prevent bubble formation and/or transfer, improve mixing, etc.).

In the depicted exemplary flow cell 40, an optional port 42 may be provided such that delivery of substances directly into the preparation chamber may be effected. For example, port 42 may preferably be used to introduce a test sample into the preparation chamber 28. The port 42 may preferably include, e.g., an external structure designed to mate with a test sample delivery device, e.g., a Luer lock fitting, threading, etc. The fluid pathway through port 42 may include an optional valve 43 to control introduction of the test sample (or other material) into the preparation chamber 28. The valve 43 may, in some instances be, e.g., a one-way valve such that materials in the

preparation chamber 28 are restricted from traveling out of the preparation chamber 28 through the port 42. Although only one port 42 is depicted, it should be understood that two or more separate ports may be provided into the preparation chamber 28.

The exemplary flow cell 40 may also preferably include one or more fluid modules 50 that mate with the flow cell 40. The modules 50 may be used to, e.g., store liquids (e.g., wash buffers, etc.), reagents, magnetic particles, etc. The fluid module or modules 50 each preferably include an opening 52 through which materials in the fluid modules 50 can be introduced into the preparation chamber 28. Control over the introduction of materials from the fluid modules 50 into the preparation chamber 28 may be obtained in a number of manners, e.g., the opening 52 may include a seal, valve, etc. Furthermore, one or more fluid modules may be operated to introduce materials simultaneously or serially into the preparation chamber 28 as desired.

One example of a fluid module 150 is depicted in the cross-sectional view of FIG. 4. The depicted exemplary fluid module 150 includes multiple sub-chambers, each of which may contain the same or different materials. It may be preferred that the fluid module 150 be designed such that the materials within the different sub-chambers mix as they are introduced to each other.

By storing the different materials within separate sub-chambers, it may be possible to provide materials in the fluid module 150 that are preferably not mixed until needed. For example, some biological substances may preferably be stored in a dry state to, e.g., prolong their shelf life, usable life, etc. To use the biological material, it must often be mixed in water or other aqueous solutions to provide a usable product. By providing the ability to mix these materials on demand, the fluid module can provide a convenient storage and introduction device for many different materials.

The depicted fluid module 150 includes three sub-chambers 154, 156 and 158. The sub-chambers are separated by seal 155 (located between sub-chambers 154 and 156) and seal 157 (located between sub-chambers 156 and 158). The fluid module 150 also includes plunger 151 with an actuator 153 that, in the depicted embodiment, is designed to pierce seals 154, 156 and 158 as the plunger 151 is moved towards opening 152 in the fluid module 150 (as indicated by the arrow in FIG. 3). The plunger 151 may preferably include an o-ring (depicted) or other sealing structure to prevent materials in the sub-chambers from moving past the plunger 150 in the opposite direction.

FIG. 5 depicts the operation of fluid module 150, with the actuator 153 having pierced seal 155 such that the materials in sub-chambers 154 and 156 can mix. It may be preferred that sub-chamber 154 contain a liquid 160, e.g., water, saline, etc. and that sub-chamber 156 contain a dried-down reagent 162 (e.g., a lysing agent, fibrinogen, etc.), with the liquid 160 causing the reagent 162 to enter into a solution or a mixture with the liquid 160. Although reagent 162 is depicted as being dried-down within sub-chamber 156, it may be located in, e.g., a powder, gel, solution, or any other form. Regardless of the form of the materials in the sub-chambers 154 and 156, piercing or opening of the seal 155 allows the two materials to contact each other and preferably begin mixing within fluid module 150.

As the plunger 151 is advanced towards the opening 152, the actuator 153 also preferably pierces seal 157 such that the materials 164 in the sub-chamber 158 can mix with materials 160 and 162 from sub-chambers 154 and 156.

When fully advanced towards the opening 152, the actuator 153 may preferably pierce seal 159 provided over opening 152, thereby releasing the materials 160, 162 and 164 from fluid module 150 and into, e.g., a preparation chamber or other space. It may be preferred that the shape of the plunger 151/actuator153 mate with the shape of the final sub-chamber 158/opening 152 such that substantially all of the materials in the various sub-chambers are forced out of the fluid module 150.

The plunger 151 in fluid module 150 may be moved by any suitable device or technique. For example, the plunger 151 may be driven by a mechanical device inserted into fluid module 150 through driver opening 168 or fluid pressure may be introduced into fluid module 150 through driver opening 168 to move the plunger 151 in the desired direction. It may be preferred to drive the plunger 151 using, e.g., a stepper motor or other controlled mechanical structure to allow for enhanced control over the movement of plunger 151 (and any associated structure such as, e.g., actuator 153). Other means for moving plunger 151 will be known to those skilled in the art, e.g., solenoid assemblies, etc.

The fluid module 150, plunger 151 and actuator 153 may be constructed of any suitable material or materials, e.g., polymers, metals, glasses, silicon, ceramics, etc. that provide the desired qualities or mechanical properties and that are compatible with the materials to be stored in the fluid modules. Similarly, the seals 155, 157 and 159 may be manufactured of any suitable material or materials, e.g., polymers, metals, glasses,

etc. For example, the seals may preferably be manufactured from polymer film/metallic foil composites to provide desired barrier properties and compatibility with the various materials to be stored in the fluid module 150.

It may be preferred that the materials used for both the seals and the fluid module housing be compatible with the attachment technique or techniques used to attach the seals in a manner that prevents leakage between the different sub-chambers. Examples of some attachment techniques that that may be used in connection with fluid modules 150 include, e.g., heat sealing, adhesives, chemical welding, heat welding, ultrasonic welding, combinations thereof, etc. It should also be understood that the fluid modules may be constructed such that the seals are held in place by friction, compression, etc.

Returning to FIG. 3, control over fluid flow across the detection surface 32 may be beneficial to control flow rate, reduce or prevent bubble formation, improve the likelihood of complete coverage of the detection surface 32, etc. In some instances, it may be desirable to control the shape of the wavefront of the liquid containing the target biological analyte. Optional features that may be provided in detection chamber 30 to assist in flow control may include, e.g., surface coatings (e.g., hydrophobic, hydrophilic, etc.), surface structures, etc. These features may, e.g., preferably be provided on the surface 38 of detection chamber 30 that faces the detection surface 32. Furthermore, one or more features may be provided in combination, e.g., surface coatings and surface structures, etc.

FIGS. 6A, 6B and 6C depict some potential surface structures that may be used for flow control over the detection surface. FIG. 6A depicts a flow control surface 138 that includes a series of triangular channels 139 spaced apart across the surface 138. Although the depicted channels 139 are parallel to each other and extend in a straight line that is perpendicular to the desired fluid flow (see arrow in FIG. 6A), it will be understood that variations in any of these characteristics may be used if they assist in obtaining the desired flow across the detection surface. For example, the channels may be irregularly sized, irregularly shaped, irregularly spaced, straight, curved, oriented at other than a ninety degree angle to fluid flow, etc.

FIG. 6B depicts another variation in which the channels 239 on flow control surface 238 have a different shape, i.e., are more rectangular as opposed to the triangular channels of FIG. 6A. In addition to the variations described above with

respect to FIG. 6A, another variation may be that channels of different shapes may be provided on a single flow control surface, e.g., a mix of triangular and rectangular channels may be provided.

FIG. 6C depicts another variation in which the flow control surface 338 includes channels 339a in a first section that are oriented at an angle that is not perpendicular to the fluid flow, while channels 339b in second section of the flow control surface 338 are oriented perpendicular the fluid flow direction (see the arrow in FIG. 6C). Such an arrangement may be beneficial in ensuring fluid flow to the sides of the surface 338 and may also shunt or direct bubbles to the edges of the detection chamber where they may not interfere with operation of the detection surface.

FIG. 6D depicts yet another surface feature arrangement for a flow control surface 438 that includes discrete structures, e.g., posts, embedded or attached beads, etc., in place of or in combination with channels as depicted in FIGS. 6A-6C. The discrete structures may be provided in any shape, e.g., circular cylinders, rectangular prisms, triangular prisms, hemispheres, etc.

Returning to FIG. 3, the flow cell 40 may also include an optional waste chamber 70 into which materials flowed across the detection surface 32 are directed. The waste chamber 70 may preferably include, e.g., an absorbent material 72 to, e.g., pull fluid through the detection chamber 30 and into waste chamber 70. Examples of suitable absorbent material 72 may include, e.g., hydrophilic materials (e.g., foams, nonwovens, etc.).

In addition to or in place of absorbent material 72, the fluid path from the detection chamber 30 to the waste chamber 70 may also include, e.g., a flow control device such as, e.g., a flow restrictor 74. Such a flow restrictor 74 may be useful if the absorbent material within the waste chamber 70 could result in fluid flow across detection surface 32 that is faster than desired. One potential example of a suitable flow restrictor 74 may be, e.g., a permeable membrane.

One example of suitable flow rates through the detection chamber 30 may be, e.g., a flow rate of 0.03 milliliters/minute for a sample volume of, e.g., 500 microliters. The actual flow rates and sample volumes will, however, vary depending on many different factors.

Another flow control feature that may be used to control fluid flow rate through the detection chamber includes, e.g., capillary structures in which the radius and length

of the capillary channel or channels controls pressure drop and, thus, flow rate through the channel or channels.

Additional descriptions and/or examples of these and other potential flow cell designs and discussions of the various features that may be optionally found in such designs may be described in attached Appendix A, entitled "Integrated Biosensor."

SYSTEM DESIGN

It may desirable that the flow cell 40 be capable of docking with or being connected to a unit that may, e.g., provide a variety of functions such as providing power to the sensors in the flow cell, accepting data generated by the sensor, providing the ability to take user input to control fluid flow and/or sensor operation within the flow cell, etc.

One such system 100 is schematically depicted in FIG. 7, and may preferably include a power source 101 and user interface 102 (e.g., pushbuttons, keyboard, touchscreen, microphone, etc.). The system 100 may also include an identification module 103 adapted to identify a particular flow cell 140 using, e.g., barcodes, radio-frequency identification devices, mechanical structures, etc.

The system 100 may also preferably include a sensor analyzer 104 that obtains data from a sensor in the flow cell 140 and a processor 105 to interpret the output of the sensor. In other words, sensor analyzer 104 may receive output from a sensor in flow cell 140 and provide input to processor 105 so that the output of the sensor can be interpreted.

Processor 105 receives input from sensor analyzer 104, which may include, e.g., measurements associated with wave propagation through or over an acousto-mechanical sensor. Processor 105 may then determine whether a target biological analyte is present in a sample. Although the invention is not limited in this respect, the sensor in flow cell 140 may be electrically coupled to sensor analyzer 104 via insertion of the flow cell 140 into a slot or other docking structure in or on system 100. Processor 105 may be housed in the same unit as sensor analyzer 104 or may be part of a separate unit or separate computer.

Processor 105 may also be coupled to memory 106, which can store one or more different data analysis techniques. Alternatively, any desired data analysis techniques may be designed as, e.g., hardware, within processor 105. In any case,

processor 105 executes the data analysis technique to determine whether a detectable amount of a target biological analyte is present on the detection surface of a sensor in flow cell 140.

By way of example, processor 105 may be a general-purpose microprocessor that executes software stored in memory 106. In that case, processor 105 may be housed in a specifically designed computer, a general purpose personal computer, workstation, handheld computer, laptop computer, or the like. Alternatively, processor 105 may be an application specific integrated circuit (ASIC) or other specifically designed processor. In any case, processor 105 preferably executes any desired data analysis technique or techniques to determine whether a target biological analyte is present within a test sample.

Memory 106 is one example of a computer readable medium that stores processor executable software instructions that can be applied by processor 105. By way of example, memory 106 may be random access memory (RAM), read-only memory (ROM), non-volatile random access memory (NVRAM), electrically erasable programmable read-only memory (EEPROM), flash memory, or the like. Any data analysis techniques may form part of a larger software program used for analysis of the output of a sensor in flow cell 140 (e.g., LABVIEW software from National Instruments Corporation, Austin, Texas).

Further descriptions of systems and data analysis techniques that may be used in connection with the present invention may be described in, e.g., U.S. Patent Application No. _____, filed on even date herewith, titled ESTIMATING PROPAGATION VELOCITY THROUGH A SURFACE ACOUSTIC WAVE SENSOR (Attorney Docket No. 58927US002) and in the attached Appendix A entitled "Integrated Biosensor." Although these documents describe systems and methods related to the use of surface acoustic wave sensors, it should be understood that the use of these systems and methods may be used with other acousto-mechanical sensors as well.

MANUFACTURING ACOUSTO-MECHANICAL SENSORS

As discussed herein, the present invention relies on the use of acousto-mechanical sensors to detect the presence of target biological analyte within a test sample flowed over a detection surface. Coating or otherwise providing the various

materials needed to provide acousto-mechanical sensors with the desired selective attachment properties may be performed using a variety of methods and techniques.

One example of a potentially useful construction is depicted in FIG. 8 and includes a substrate 80 on which a waveguide 82 is located. A tie layer 84 may be provided between an immobilization chemistry layer 86 and waveguide 82 if necessary to, e.g., obtain the desired level of adhesion between those layers (or to achieve some other result). A layer of capture agents 88 may be provided on the immobilization layer 86 and, in some embodiments, a passivation layer 90 may be provided over the layer of capture agents 88.

Various materials for the different components illustrated in FIG. 8 may be described herein (or in the attached appendices). Applying these layers may involve the use of conventional techniques such as, e.g., spin coating, etc. In some instances, however, it may be desirable to use alternative techniques such as, e.g., pattern coating, ink jet coating, etc. Some potential pattern coating techniques may be described in, e.g., U.S. Patent Application No. 10/607698, filed June 27, 2003, entitled PATTERNED COATING METHOD (Attorney Docket No. 58399US002).

Some potentially suitable ink jet coating techniques may be described in, e.g., attached Appendix C, entitled "Inkjet Printing on Acousto-Mechanical Sensors."

As used herein and in the appended claims, the singular forms "a," "and," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a target biological analyte" includes a plurality of target biological analytes and reference to "the detection chamber" includes reference to one or more detection chambers and equivalents thereof known to those skilled in the art.

All references and publications identified herein (and/or identified in the attached appendices) are expressly incorporated herein by reference in their entirety into this disclosure. Illustrative embodiments of this invention are discussed and reference has been made to possible variations within the scope of this invention. These and other variations and modifications in the invention will be apparent to those skilled in the art without departing from the scope of the invention, and it should be understood that this invention is not limited to the illustrative embodiments set forth herein. Accordingly, the invention is to be limited only by the claims provided below and equivalents thereof.

CLAIMS:

1. A method of detecting a biological analyte, the method comprising:

contacting a test sample with a selective mass modifier, wherein a target biological analyte within the test sample interacts with the selective mass-modifier such that a mass-modified target biological analyte is obtained within the test sample;

contacting a detection surface of a shear horizontal surface acoustic wave device with the mass-modified test sample;

selectively attaching the mass-modified target biological analyte to the detection surface; and

operating the shear horizontal surface acoustic wave device to detect the attached mass-modified biological analyte.

2. A method according to claim 1, wherein the selective mass modifier comprises a lysing agent, and wherein the mass-modified biological analyte comprises fractionated biological analyte.

3. A method according to claim 1, wherein the selective mass-modifier comprises fibrinogen.

4. A method according to claim 1, wherein the selective mass-modifier comprises magnetic particles.

5. A system for detecting a target biological analyte, the system comprising:

a shear horizontal surface acoustic wave sensor comprising a detection surface in a detection chamber;

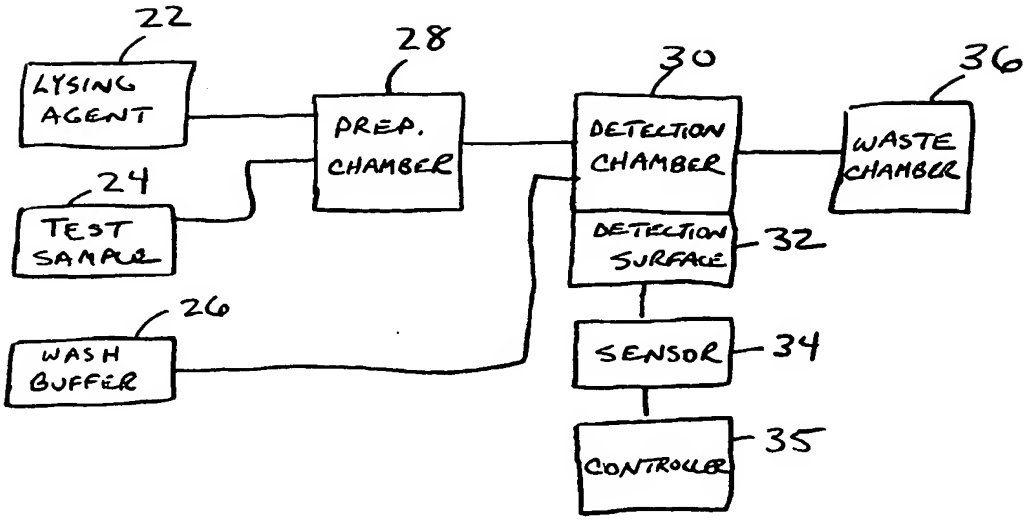
a capture agent located on the detection surface, wherein the capture agent is capable of selectively attaching the target biological analyte to the detection surface;

one or more fluid modules in selective fluid communication with the detection chamber, wherein material within the one or more fluid modules can be selectively introduced into the detection chamber;

means for driving the shear horizontal surface acoustic wave sensor;

means for analyzing data from the shear horizontal surface acoustic wave sensor to determine if the target biological analyte is coupled to the capture agent; and

means for drawing fluid across the detection surface of the shear horizontal surface acoustic wave sensor.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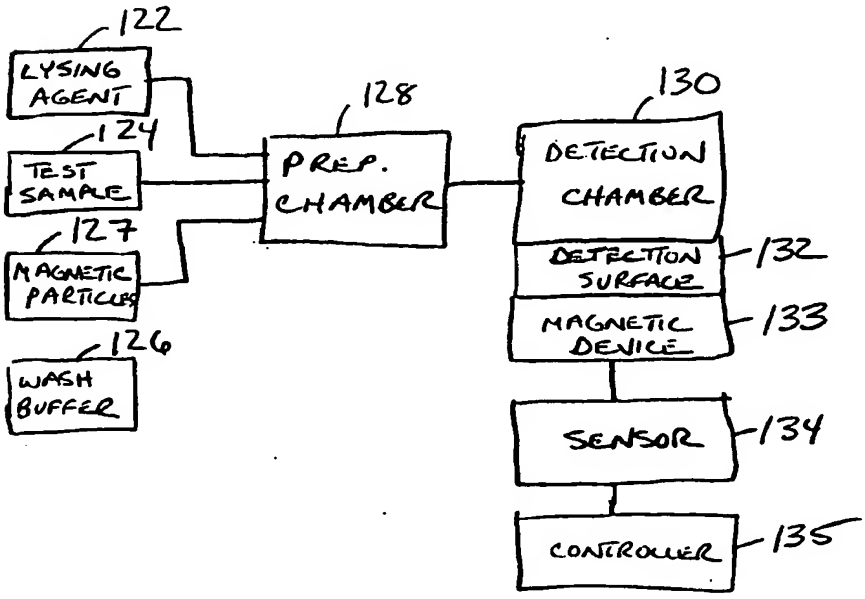
28
PREP. CHAMBER
30
DETECTION CHAMBER
36
WASTE CHAMBER
24
TEST SAMPLE
DETECTION SURFACE
32
26
WASH BUFFER
SENSOR
34
CONTROLLER
35

FIG. 1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128
130
124
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PREP. CHAMBER
DETECTION CHAMBER
127
DETECTION SURFACE
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MAGNETIC DEVICE
133
126
WASH BUFFER
SENSOR
134
CONTROLLER
135

FIG. 2

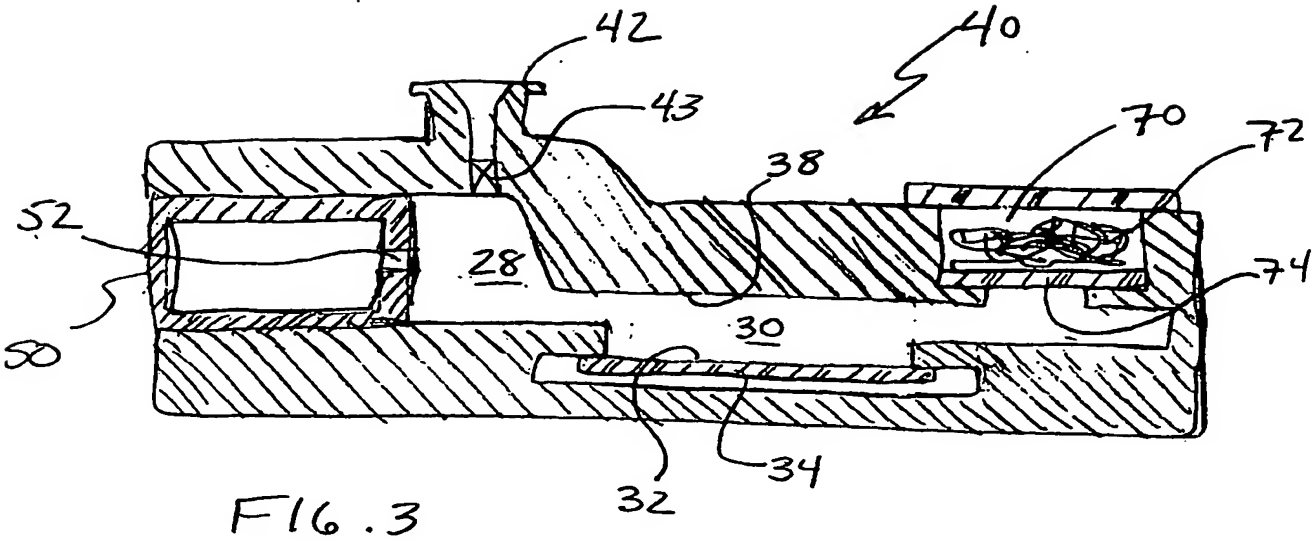

FIG. 3

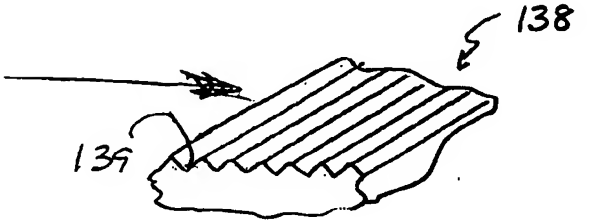

FIG. 6A

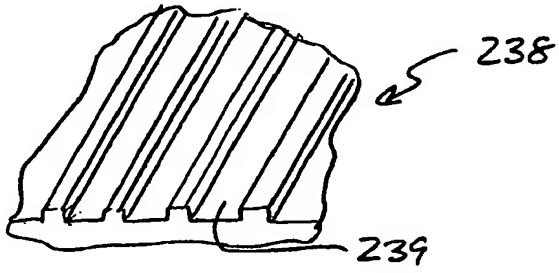

FIG. 6B

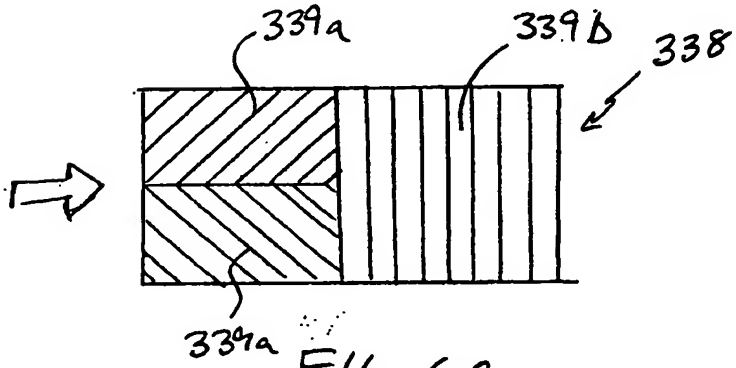

FIG. 6C

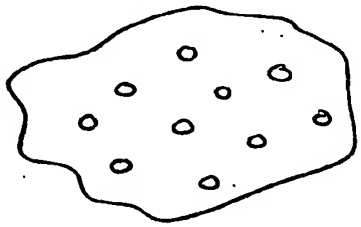

FIG. 6D

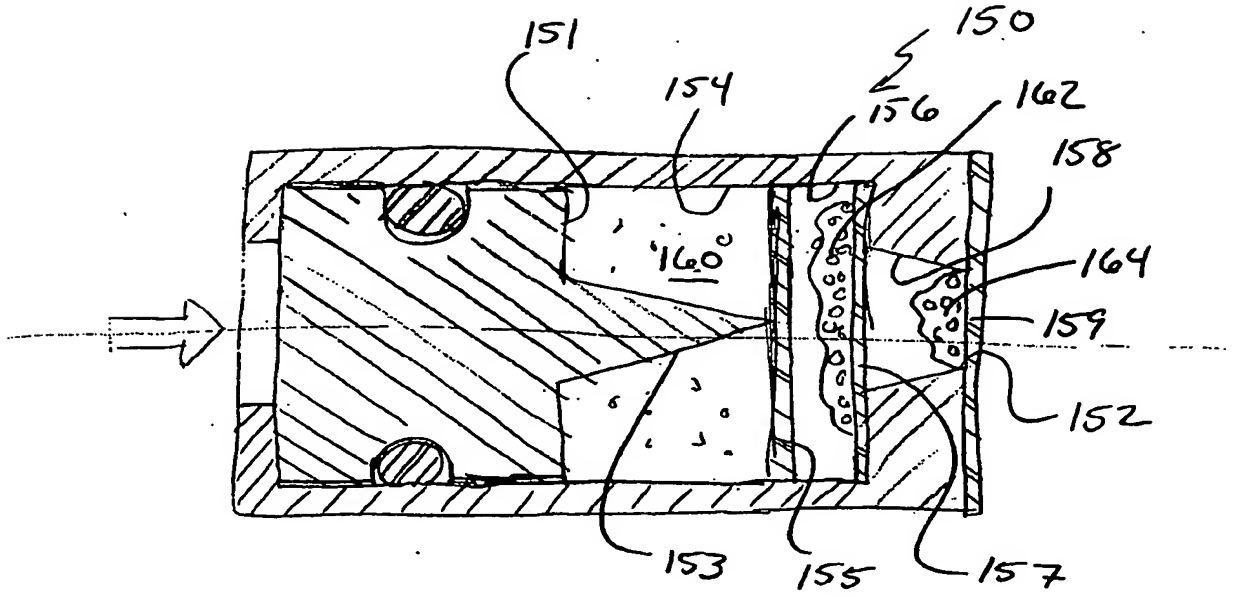
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FIG 4

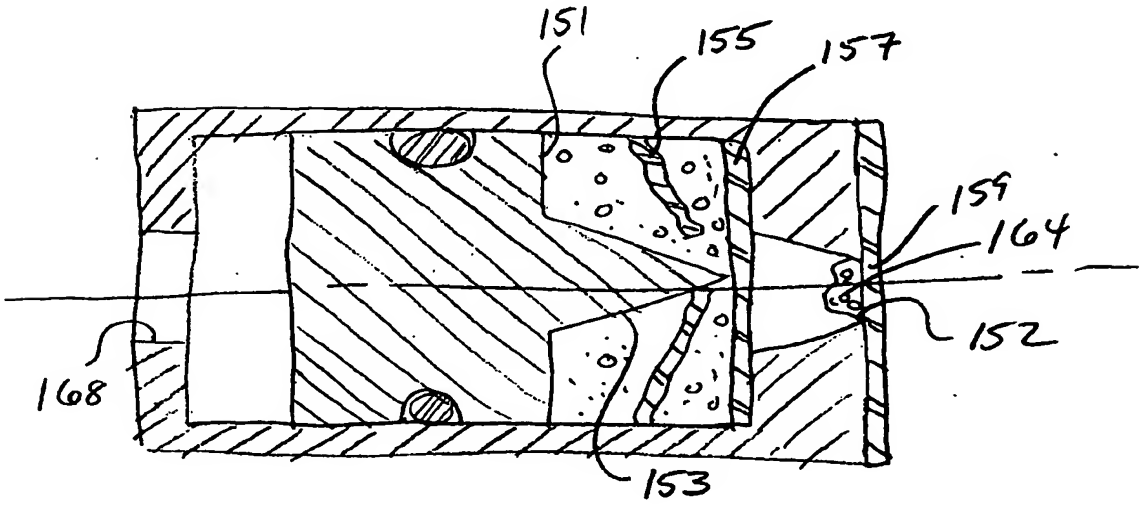
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FIG 5

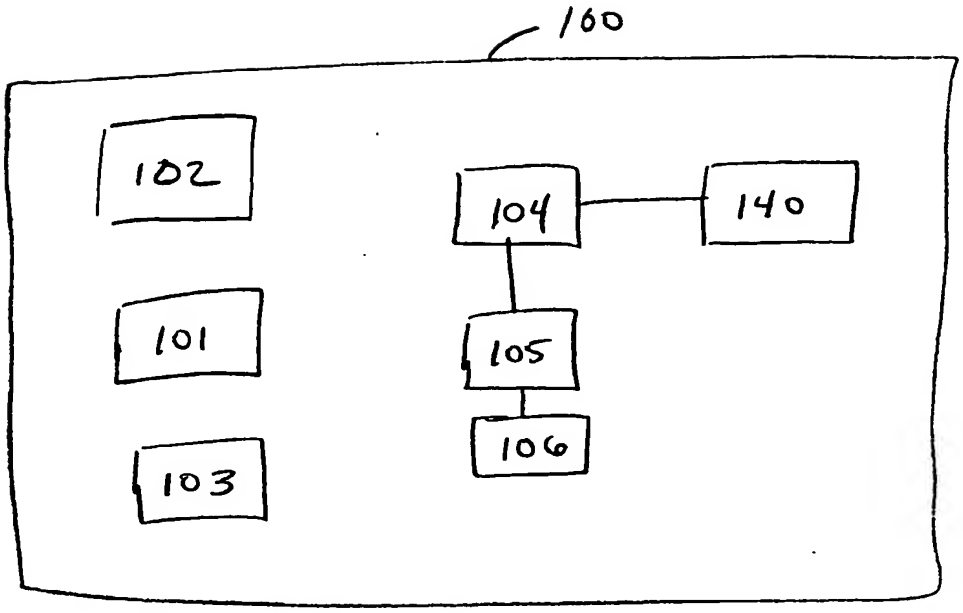

FIG. 7

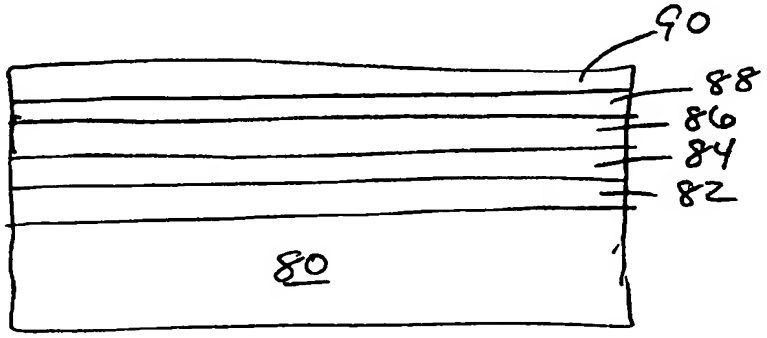

FIG. 8

Document made available under the Patent Cooperation Treaty (PCT)

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International filing date: 17 December 2004 (17.12.2004)

Document type: Certified copy of priority document

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Number: 60/533,169
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